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## A single dose of nicotine may be sufficient to induce tyrosine hydroxylase in noradrenergic neurones.

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We have recently reported that nicotine given to rats increases catecholamine synthesis, in a regionally selective manner, in brain areas in which increased catecholamine release can be demonstrated with *in vivo* techniques (1,2). We have also shown (3) that repeated daily injections of nicotine for between 3 and 28 days increase the activity of tyrosine hydroxylase (TH), the rate limiting enzyme in catecholamine biosynthesis, in noradrenergic neurones. The early response seen in the cell bodies in the locus coeruleus is followed by increases in the terminal regions (cerebellum, hypothalamus, hippocampus and frontal cortex) over a time course related to the distance of the terminals from their cell bodies. The increase in TH activity in the terminals seems to be independent of continued nicotine administration once an increase in enzyme activity in the locus coeruleus is established with 7 days of treatment (4). We now report the effect of a single dose of nicotine on TH activity in these neurones over a similar time scale.

Nicotine bitartrate (0.8mg/kg as free base), neutralised in isotonic saline, or saline alone was given to groups (n=6) of male Sprague-Dawley rats by subcutaneous injection. Animals were sacrificed on the seventh day after injection for the cell body regions or on the 21st day for the terminals. The locus coeruleus, hypothalamus and hippocampus were removed by dissection from slices prepared using razor blades and an aluminium guide block, then frozen in liquid nitrogen pending analysis. Samples were thawed and homogenised, then assayed for TH activity using a method described in (2) in which $^{3}$H-tyrosine was supplied as substrate, 6-methyltetrahydropterin as cofactor and ascorbate as reductant. The product, $^{3}$H-DOPA, was isolated on alumina columns.

A single injection of nicotine on the first day or on the first two days resulted in TH activities in the locus coeruleus 7 days later of 232% and 250% of saline controls respectively. This compares with an increase to 223% of controls after 7 days of repeated nicotine administration (3). 21 days after a single dose of nicotine, TH activities had increased to 157% of controls in the hippocampus and to 136% in the hypothalamus, compared with 180% and 147% respectively following 21 days of repeated nicotine injection.

The effects of chronic nicotine on TH activity in noradrenergic neurones are analogous to those after a single dose of reserpine (5). Reserpine has been shown to increase TH mRNA (6), suggesting that induction in the cell bodies followed by axonal transport, rather than activation, underlies the increase in enzyme activity. These results imply that subchronic administration of nicotine, or as few as one or two doses, are as effective as chronic nicotine in increasing TH activity. We have observed (3) that the increases in enzyme activity are not sustained even with chronic nicotine administration. This might be due to desensitisation after initial exposure to the drug.

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